HIGHLY SENSITIVE C-REACTIVE PROTEIN CONCENTRATION AND ANGIOGRAPHIC CHARACTERISTICS OF CORONARY LESION

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Background: The role of inflammation in all stages of atherosclerotic disease is increasingly recognized especially in last few years. The chronic inflammatory process can develop to an acute clinical event by the induction of plaque rupture and therefore cause acute coronary syndrome. C-reactive protein is a strong predictor of clinical outcome in coronary artery disease and inflammation has been implicated in the process. We aimed to evaluate the relationship between pre-procedural highly sensitive C-Reactive Protein (hs-CRP) and angiographic features in patients with acute coronary syndrome. **Methods:** In a cross-sectional study, we examined 100 patients admitted with acute coronary syndrome and assessed the relationship between preprocedural hs-CRP concentration and coronary angiographic lesions. **Results:** One hundred patients with acute coronary syndrome were assessed. Some of the results were as follows: mean age 59.26±11.04, 64% male and 36% female. 34% of patients had unstable angina, 43% had Non ST elevation myocardial infarction (NSTEMI) and 23% had ST elevation myocardial infarction (STEMI). The mean value of hs-CRP was 4.26±1.42 mg/dl with highest values in patients eccentric/irregular lesion and patients having macroscopic thrombus (p=0.01). **Conclusion:** Among patients with acute coronary syndrome increased levels of hs-CRP correlates with specific high risk coronary artery lesions.
Keywords: Highly sensitive C-reactive protein, Angiographic lesion, Acute coronary syndrome.

INTRODUCTION

Inflammation of vessel wall is now considered to play an essential role in the initiation and progression of atherosclerosis[1] and also in its final steps, i.e., plaque erosion or fissure and eventually plaque rupture.[2,3] There is increasing evidence that it applied to pathophysiology of acute coronary syndrome. In particular, increased C-reactive protein (CRP), an acute phase reactant has been associated with unstable angina[4] and favourable short and long term clinical outcomes in patients with coronary artery disease.[5] CRP, a major acute phase response protein synthesized in the liver in response to the acute phase cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor alpha(TNF-alpha). Inflammation may determine plaque stability, unstable plaques have increased leukocyte infiltrates, T-cell, macrophages predominate rupture sites. Cytokines and metalloproteinase influences both stability and degradation of fibrous cap. Infectious pathogens, including Chlamydia pneumoniae and cytomegalovirus have been implicated as mediators of coronary inflammation, but the data is controversial.[6] The normal serum concentration of CRP ranges from 3 mg/dl to more than 200 mg/dl. Because these ranges are not sensitive for the values required to determine cardiovascular risk in otherwise healthy person, investigators have developed new modified techniques to measure highly sensitive CRP. The hs-CRP assay has been shown to detect concentration below 0.2 mg/dl and uses monoclonal or polyclonal anti-CRP antibodies in an enzyme-linked immunoabsorbent assay (ELISA) or immunoflorescent.[7] hs-CRP levels correlate with the clinical severity of coronary artery disease and with coronary events in both acute and subacute phase of myocardial ischemia. Patients who are hospitalized for treatment of acute coronary syndrome and have raised CRP levels have significantly more ischemic episodes during hospital stay then patients with lower CRP levels.[8] Among patients with suspected coronary artery disease undergoing coronary angiography, increased CRP is strongly associated with specific high risk features of culprit coronary artery lesions.[9] A recent study from Zairis and colleagues reported that hs-CRP concentration correlate with stenosis complexity in patients with acute coronary syndrome.[10] In patients with acute coronary syndrome increased CRP level is associated with presence of complex angiographic lesions and the need for revascularization.[11] It has been recently reported that hs-CRP correlate with number of vulnerable plaques and such patients also have increased risk of future coronary events.[12] CDC/AHA defines the relative risk categories of patients according to their hs-CRP levels as low, average and high (<1.0 mg/dl, 1.0–3.0 mg/dl, >3.0 mg/dl respectively).[13] This study is conducted to evaluate relationship between pre-procedural hs-CRP and angiographic features in patients with acute coronary syndrome.

METHODS

This was a cross sectional study, which was conducted at department of Cardiology Liaquat National Hospital

Karachi. One hundred consecutive patients of both genders above 30 years of age admitted with acute coronary syndrome were enrolled after taking informed consent. Patients with history of any rheumatologic disease and those who had history of infectious process within 2 weeks prior to catheterization were excluded. Detailed history and physical examination was done. The aim of study was to assess the association of preprocedural Hs-CRP concentration in patients with acute coronary syndrome and angiographic features of coronary lesions.

Acute coronary syndrome was defined as prolonged (>20 min) ischemic chest pain in preceding 24 hrs associated with transient ischemic changes on ECG with or without raised level of biochemical markers of myocardial damage.

Coronary lesions were classified as discrete long >10 mm, eccentric/irregular, with macroscopic thrombus and total occlusion according to American College of Cardiology/ American Heart Association nomenclature.[14]

Blood samples for Hs-CRP were drawn during admission and analyzed with chemiluminescent immunometric assay. Coronary angiography was performed according to standard technique via right femoral approach.

Data was analyzed by SPSS version 10. Descriptive statistics were used to calculate frequencies and percentages of different clinical presentations, risk factors and coronary angiographic findings of patients. Mean±SD was calculated for age and hs-CRP levels. Relationship between hs-CRP levels and characteristic of coronary artery lesion was calculated using chi-square test.

RESULTS

A total of 100 patients (64% male) with acute coronary syndrome were studied. 34% had unstable angina, 43% had NSTEMI and 23% had STEMI. Data is given in table 1. Mean hs-CRP was 4.26±1.96 mg/dl as shown in Figure-1.

Table-1: Demographic data

Age (yrs) mean±SD	59.26±11.04
Male	64 (64%)
Female	36 (36%)
Risk Factors	
Diabetes	55 (55%)
Hypertension	66 (66%)
Smoking status	
Current smoker	24 (24%)
Past smoker	12 (12%)
Never smoked	64 (64%)
History of coronary artery disease	43 (43%)
History of previous coronary artery intervention	
PCI	15 (15%)
CABG	12 (12%)

In patients with unstable angina Hs-CRP was 3.12±1.62 mg/dl, with NSTEMI it was 4.38±1.51 mg/dl and with STEMI it was highest 5.77±2.15 mg/dl. Most of the patients with STEMI and NSTEMI had hs-CRP values >4 mg/dl, putting them in high risk category, shown in Table-2.

Coronary angiographic findings of patients are given in Table-3. The hs-CRP levels were found to be associated with culprit lesion morphology. Patients with macroscopic thrombus had highest hs-CRP levels, i.e., 5.88±1.73 mg/dl while with eccentric lesions it was 3.77±1.66 mg/dl, for long lesions 2.87±1.66 mg/dl and in patients with total occlusion it was 3.44±2.11 mg/dl (p=0.01) as shown in Figure-2.

Higher number of patients with irregular lesions and macroscopic thrombus has hs-CRP levels >4 mg/dl, i.e., high risk category, as shown in Table-4.

Table-2: Levels of hs-CRP USA, NSTEMI, STEMI

hs-CRP levels mg/dl	USA	NSTEMI	STEMI
<1–2	9	2	0
2–4	12	16	5
>4	13	25	18

Table-3: Characteristic of culprit lesion

Long (>10mm)	8 (8%)
Eccentric/irregular	60 (60%)
Macroscopic thrombus	28 (28%)
Total occlusion	4 (4%)

Table-4: Level of hs-CRP in different lesions

hs-CRP level mg/dl	Long lesions	Irregular lesions	Macroscopic thrombus	Total occlusion
<1–2	3	9	0	1
2–4	4	25	5	3
>4	1	26	23	0
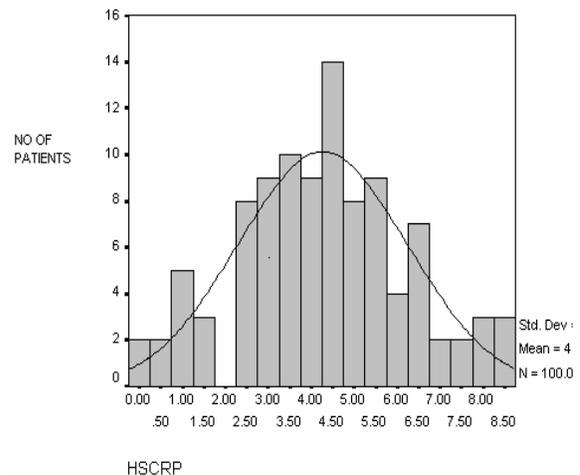
Figure-1: Level of hs-CRP in patients.

Box Plots for hsCRP concentration in patients with various angiographic lesions
Group 1 Long lesions , Group 2 Irregular/eccentric lesions,
Group 3 Lesions with macroscopic thrombus, Group 4 Total occlusion.

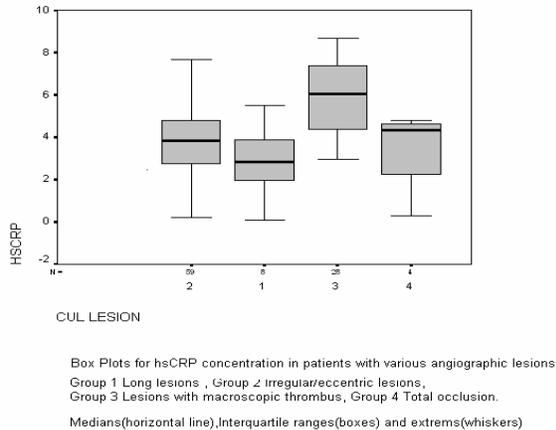Medians(horizontal line),Interquartile ranges(boxes) and extrems(whiskers)

Figure-2: hs-CRP concentration in patients with various angiographic lesions

DISCUSSION

In a cohort of consecutive patients undergoing cardiac catheterization for suspected CAD, CRP concentrations were strongly associated with a clinical presentation of acute syndrome and with distinct angiographic features of the lesions suggestive of acute pathophysiology. Our findings strengthen the hypothesis that acute inflammation is a component of the pathophysiology of coronary syndromes. Our study was the first done study in Pakistan to link hs-CRP concentration with lesion morphology and acute coronary syndrome. Lesions in our study were defined by AHA/ACC nomenclature. Total occlusions are associated with a decreased chance of successful percutaneous transluminal coronary angioplasty; they do not necessarily reflect an acute process. In fact totally occluded lesion means completed events, so they may have no active inflammatory component and therefore no significant increase in CRP values is expected.

It was clearly shown in our study that high number of patients with STEMI and NSTEMI had high hs-CRP levels, i.e., >4 mg/dl suggesting active inflammatory process. Our results suggest that CRP is not only a marker of vascular inflammation but may also play an important key role in plaque disruption leading to STEMI and NSTEMI. Our findings that hs-CRP serum level is increased in patients with acute coronary syndrome and correlates with angiographic lesions in these patients support to a role of CRP in plaque vulnerability. Another study done by Espligureal R *et al*, showed that, hs-CRP was significantly higher in patients with acute coronary syndrome compared to chronic stable angina (p=0.004) and correlate with complex angiographic lesion (p=0.001).[15]

Moukarbel and colleagues studied the correlation between CRP and complexity of coronary lesions in unstable angina patients. The percent of patients with elevated CRP was 56% in the group with low complexity culprit lesions, 84% in intermediate and 93% in the high complexity culprit lesion groups. The investigators concluded that elevated CRP levels on admission are a marker for anatomic complexity of culprit lesions.[11]

Angiography offers only visual information and has limitations. For example, we could only assess the presence of macroscopic thrombi, whereas microscopic thrombi are not uncommon. Vulnerablity of plaque to rupture is related to microscopic characteristics of coronary plaques, such as increased macrophages, reduced smooth muscle cells, a large soft lipid core and thin plaque cap [16].Therefore some non critical appearing lesions may be at high risk for rupture. This would mean that true relationship between lesion morphology and CRP is probably even stronger than we observed using only coronary angiography.

CONCLUSION

However there is clear trend that hs-CRP level correlates significantly with angiographic features of thrombi and eccentric lesions. Patients with totally occluded lesions with no visible thrombus had low hs-CRP, suggesting its role as acute inflammatory marker. Patients with unstable angina had low level of hs-CRP as compared with patients with NTEMI and STEMI.

Thus inflammation can be implicated in transformation of stable coronary plaque to unstable plaque rupture and thrombus. Identification of markers indicating propensity of plaque rupture is of clinical importance and hs-CRP may be simple and useful in this regard.

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